

Docket No.: 1056-0139PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Toshihiko NAITO et al.

Application No.: 10/577,308

Confirmation No.: 5144

Filed: April 28, 2006

Art Unit: 1621

For: UREA DERIVATIVE AND PROCESS FOR
PREPARING THE SAME

Examiner: P.G. O'Sullivan

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner for Patents
P.O. Box 1450
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Sir:

I, Dr. Toshihiko Naito, declare the following:

I am an inventor of the above-identified application. My *curriculum vitae* is attached.

I am presently employed at Eisai Co., Ltd., as Director of the Active Pharmaceutical Ingredient Research Laboratories. I hold a doctorate in Pharmaceutical Sciences from Tohoku University.

I have read and understand the specification and claims of the above-identified application, the outstanding Office Action of June 26, 2008, and the cited reference Funahashi et al., U.S. Patent No. 7,253,286 (hereinafter, "Funahashi et al.").

The following experiments describe data extracted from the Funahashi et al. reference and the present specification, the disclosure of which is incorporated herein by reference. These

data provide objective evidence of unexpected results, thereby differentiating the presently claimed invention from those disclosed in Funahashi et al.

The Funahashi et al. Process

The Examiner's attention is respectfully directed to the attached Appendix A which depicts a process of Funahashi et al. which achieves production of the same final compound as produced in Examples 1-4 of the present invention (top panel). The Funahashi et al. process is disclosed in Product Examples 152-3, 366-1, 368-1 and 368. (See, Funahashi et al. at column 154, lines 51-67 (Example 152-3), column 269, line 38 to column 270, line 25 (Example 366-1), column 270, lines 53-67 (Example 368-1), column 270, lines 33-51 (Example 368)). Example 368 of Funahashi et al. produces the final product 4-(3-Chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinoline carboxamide. Funahashi et al. provide the following disclosure at column 370, lines 33-48, concerning Example 368 (the "title compound" recited in the paragraph below is the final product, 4-(3-Chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinoline carboxamide):

The title compound (22.4 mg, 0.052 mmol, 34.8%) was obtained as white crystals from phenyl N-(4-(6-carbamoyl-7-methoxy-4-quinolyl)oxy-2-chlorophenyl)carbamate (70 mg, 0.15 mmol) and cyclopropylamine, by the same procedure as in Example 11.

The procedure of Example 11, at column 108, lines 30-54, of Funahashi et al. is disclosed as the following process:

Phenyl N-(4-(6-cyano-7-(2-methoxyethoxy)-4-quinolyl)oxyphenyl)carbamate (104 mg, 0.228 mmol) was dissolved in dimethylsulfoxide (1 ml), and then 2-aminopyridine (43 mg, 0.457 mmol) was added and the mixture was heated at 85 °C for 3 hours while stirring. After cooling, ethyl acetate and water were added for distribution, and the organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After filtering off the drying agent and

concentrating under reduced pressure, ethyl acetate-hexane was added to the residue and the precipitated crystals were filtered out and dried under reduced pressure to obtain the title compound (86 mg, 0.189 mmol, 82.7%) as white crystals.

Thus, in Example 368, following the guidelines set forth in Example 11, phenyl N-(4-(6-carbamoyl-7-methoxy-4-quinolyl)oxy-2-chlorophenyl)carbamate (70 mg, 0.15 mmol) was dissolved in dimethylsulfoxide. Then cyclopropylamine was added and the mixture was heated at 85 °C for 3 hours with stirring. The same work-up was performed on the resultant product as described in Example 11.

This Funahashi et al. process provided a total yield of final product of only 25.5%. (*See*, Funahashi et al. at column 270, lines 53-67 (Example 368-1), column 270, lines 33-51 (Example 368), *i.e.* 83.7% x 87.4% x 34.8% = 25.5%).

The Process of the Present Invention

Applicants' process, as disclosed at paragraph [0048] of the present specification, is conducted as follows:

To dimethylsulfoxide (20 mL) were added 7-methoxy-4-chloro-quinoline-6-carboxamide (0.983 g), 1-(2-chloro-4-hydroxyphenyl)-3-cyclopropylurea (1.13 g) and cesium carbonate (2.71 g), followed by heating and stirring at 70°C for 23 hours. After the reaction mixture was allowed to cool down to room temperature, water (50 mL) was added, and the produced crystals were collected by filtration to give 1.56 g of the title compound (88% yield).

Applicants' process provides a total yield of final product of 67.8%, *i.e.* 77% x 88% = 67.8%. (*See*, present specification, at paragraphs [0035] to [0050]).

Comparison of Processes and Results

First, it can be seen that both process are similar in that the solvent dimethylsulfoxide is utilized in both, and both require a heating step with stirring.

Second, Applicants' process, providing a total yield of final product of 67.8%, is a marked improvement over the process of Funahashi et al., which reports a yield of only 25.5%. Thus, the present invention improves the final yield by more than 100%.

One of ordinary skill in the art would not have predicted that such a large increase in yield could be obtained by changing the process of Funahashi et al. Such unexpectedly high yields could not be predicted based on the disclosure of processes in Funahashi et al. As evidenced by the indicated objective data, the presently claimed invention therefore discloses unexpected results as compared to the Funahashi et al. process.

STATEMENT UNDER 18 U.S.C. § 1001

I hereby declare that all statements made herein of any own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: Sep. 30, 2008

A handwritten signature in black ink, appearing to read 'T. Naito', written over a horizontal line.

Dr. Toshihiko Naito

Attachments: *Curriculum vitae* of Dr. Toshihiko Naito

Appendix A – schematic comparison of the synthetic method of Funahashi et al. and the method disclosed in the present application.

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April 1979-March 1981: Graduate School of Pharmaceutical Sciences, Kanazawa University (MS in Pharmaceutical Science)

March 1986: He got Ph.D. at Graduate School of in Pharmaceutical Sciences, Tohoku University.

Employment:

April 1985-September 1996: Researcher, Eisai Co., Ltd. (Tsukuba, Japan), Basic research in Medicinal Chemistry.

Oct 1996-Marh 2006: Section Head of Process Research Laboratories

April 2006-present: Director of Active Pharmaceutical Ingredient Research Laboratories

Patents (US)

Appl. No.	Filed	Patent No.	Issue date	Title
07/107631	1987/10/13	4921850	1990/5/1	3-PROPENYLCEPHEM DERIVATIVE
07/181427	1988/4/14	4929612	1990/5/29	THIADIAZOLYLACETAMIDE CEPHEM DERIVATIVES
07/463514	1990/1/11	5066812	1991/11/19	3-PROPENYLCEPHEM DERIVATIVE
07/463518	1990/1/11	5089491	1992/2/18	3-PROPENYLCEPHEM DERIVATIVE
07/463519	1990/1/11	5006649	1991/4/9	3-PROPENYLCEPHEM DERIVATIVE
07/468319	1990/1/22	5128465	1992/7/7	PROCESS FOR THE PREPARATION OF CEPHEM DERIVATIVES AND INTERMEDIATES THEREFOR
07/768515	1991/9/26	5281626	1994/1/25	BENZENESULFONAMIDE DERIVATIVES
07/861717	1992/4/1	5373000	1994/12/13	7 β - (THIADIAZOLYL) - 2 - IMINOACETAMIDO - 3 CEPHEM COMPOUNDS
08/161817	1993/12/6	5530118	1996/6/25	BENZENESULFONAMIDE DERIVATIVES
08/382158	1995/2/1	5648372	1997/7/15	ANTIFUNGAL AGENTS, AND COMPOSITIONS
08/581257	1995/12/29	5663414	1997/9/2	BENZENESULFONAMIDE DERIVATIVES

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08/810283	1997/3/3	5789429	1998/8/4	ANTIFUNGAL AGENTS, PROCESSES FOR THE PREPARATION THEREOF, AND INTERMEDIATES
10/018688	2000/6/30	6841549	2005/1/11	CONDENSED IMIDAZOLE COMPOUNDS AND A THERAPEUTIC AGENT FOR DIABETES MELLITUS
10/577308	2004/11/8	2007/0037849		UREA DERIVATIVE AND PROCESS FOR PRODUCING THE SAME
11/920920	2006/5/25	2008/161566		INTERMEDIATE IN PRODUCTION OF [2-(3, 3, 5, 5- TETRAMETHYLCYCLOHEXYL) PHENYL]PIPERAZINE COMPOUND

Papers

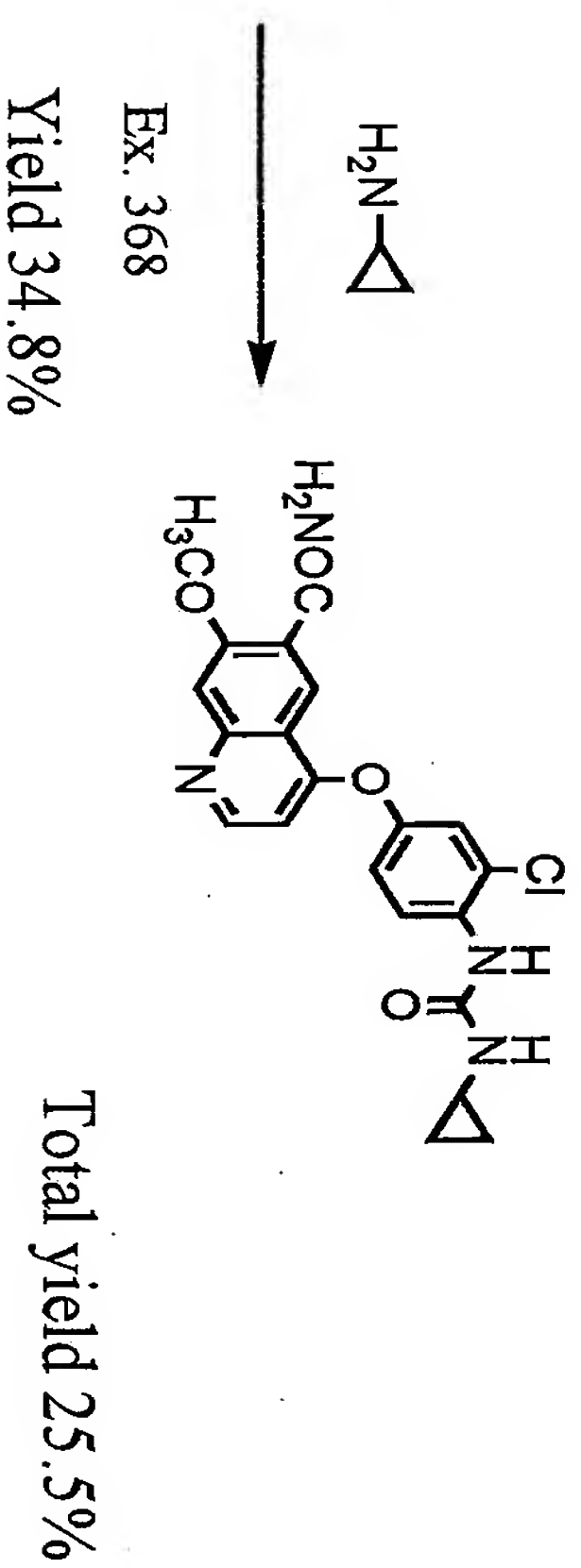
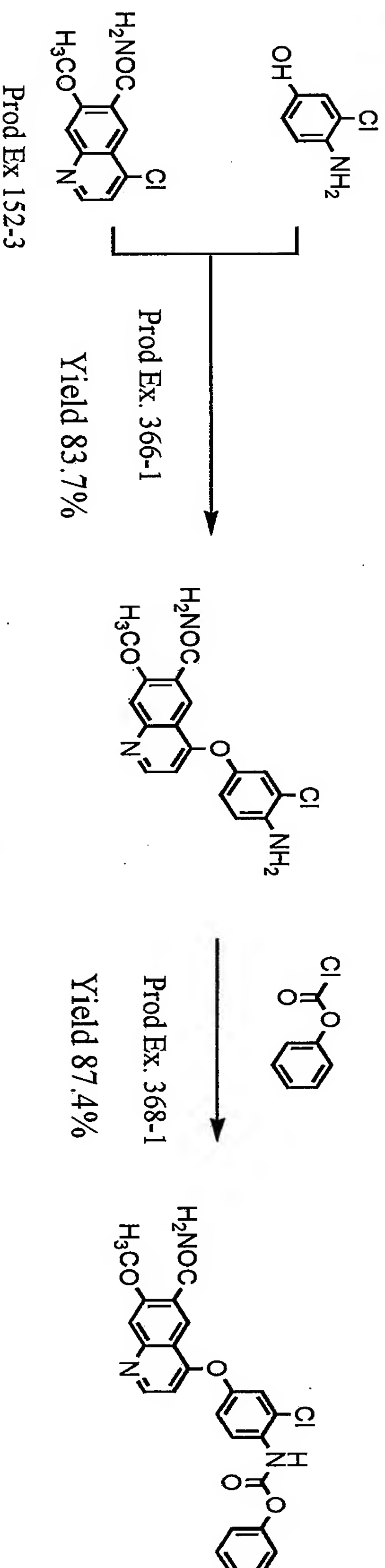
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Appendix A

US 7,253,286



USSN 10/577,308

